Comparative anticonvulsant studies on ethanol and ethyl acetate extracts of *Zingiber Officinale* Roscoe rhizome in mice and chicks

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Abstract

Epilepsy represents a major public health problem in low- and middle-income countries of Africa and Latin America where over 75% of patients do not have access to treatment. Aqueous and ethanol extracts of *Zingiber officinale* have been reported previously to have anticonvulsant effect. This study was aimed at comparing the anticonvulsant effect of ethanol and ethylacetate extracts of *Zingiber officinale* rhizomes in mice and chicks. Fresh rhizomes of *Zingiber officinale* (ginger) were collected, size reduced, air-dried under shade and extracted with ethanol and ethylacetate using cold maceration. Anticonvulsant activity of the extracts was determined by maximal electroshock stimulation (MES) in chicks, pentylenetetrazole (PTZ) and strychnine induced seizure models in mice. The ethanol and ethylacetate extracts of the ginger at doses of 50, 100 and 200 mg/kg were administered intraperitoneally 30 minutes prior to the induction of seizures. Both ethanol and ethylacetate extracts of *Zingiber officinale* at the doses of 100 and 200 mg/kg produced a dose-dependent protection against tonic hind limb extension seizure in MES model, significantly ($p<0.01$) decreased the onset of clonic seizure in the strychnine model and significantly ($p<0.001$) prolonged the mean time of death in the PTZ model. In addition, the ethanol extract at the doses of 100 and 200 mg/kg significantly ($p<0.001$) decreased the onset of seizure in the PTZ model. It might be concluded that both ethanol and ethylacetate extracts of *Zingiber officinale* contain biologically active compounds with significant anticonvulsant activity, but the ethanol extract produced a better anticonvulsant activity.

Key words: *Zingiber officinale*, anticonvulsant, MES, Pentylenetetrazole, Strychnine

Introduction

Epilepsy is a chronic disorder of the brain of various etiologies, characterized by unprovoked spontaneous recurrent seizures due to neuronal hyperactivity in the brain. It represents a major public health problem with significant economic burden, social and psychological consequences. Epilepsy affects people of all races, ages and both sexes with worldwide distribution, though, the prevalence and incidence are slightly higher in men than women and more prevalent in low and middle-income countries (WHO, 2019; Beghi, 2020). It is estimated that about 80% of epileptic patients reside in low- and middle-income countries of Africa and Latin America (Espinosa-Jovel et al., 2018). The higher prevalence of epilepsy in these regions of the world has been attributed to poverty, increased risk of endemic infectious diseases, higher incidence of road traffic and birth-related injuries, poor health infrastructures and lack of accessibility to health care (WHO, 2019).

Despite the availability of many classes of antiepileptic drugs for the management of epilepsy, over 75% of the patients in low- and middle-income countries do not have access to treatment (Espinosa-Jovel et al., 2018), hence rely on herbal medicines. About 30–40% of the patients that received treatment experience numerous adverse effects associated with the current antiepileptic drugs (Zhul et al., 2014). Also, the current antiepileptic drugs are effective in only 30–40% of the patients, neither provide a cure for epilepsy nor prevent the progression of epilepsy disease (Doeser et al., 2015; Chindo et al., 2021). Thus, there is need for continuous search for safer and more efficacious antiepileptic agents that will improve the patients 'quality of life.

Natural products like medicinal plants, when supported by credible scientific research can be sources of safe and effective drugs for prevention and treatment of many chronic diseases including epilepsy. Traditionally, these medicinal plants are utilized in form of extracts for treatment of various diseases. The solvents commonly used in extracting bioactive compounds from medicinal plants are polar and nonpolar solvents, including water, methanol, ethanol, ethylacetate, and others (Truong et al., 2019; Abubakar and Haque, 2020). Rhizome of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has been used as spice, flavouring agent and in many traditional medicines for its health-promoting properties. Previous studies reported that aqueous and ethanol extracts of ginger have anticonvulsant effect (Hosseini and Mirazi, 2015; Hosseini et al., 2016; Yakubu et al., 2019). The present study aimed at comparing the anticonvulsant effect of ethanol (polar solvent) and ethylacetate (nonpolar solvent) extracts of *Zingiber officinale* (ginger).

Materials and Methods

Plant material

The fresh rhizomes of *Zingiber officinale* (ginger) were collected in October, 2019 from a farm at Jaba local government area of Kaduna state, Nigeria. The plant was identified, confirmed and authenticated by a taxonomist, Namadi Sanusi of the Department of Botany, Faculty of Life Sciences, Ahmadu Bello University, Zaria, Kaduna State, Nigeria with Voucher specimen (Number 2099).

Experimental animals

Swiss albino mice (22-28) and day old chicks were used in the study. The mice were procured from the animal house facility of the

Department of Pharmacology and Toxicology, Kaduna State University, while the day old chicks were obtained from Olam farm, Kaduna. The mice had free access to food and water *ad libitum* and maintained under standard hygienic conditions. All experiments were carried out in accordance with the standard protocols of National Institute of Health (NIH, 2008) guidelines for use and care of laboratory animals.

Preparation of plant extract

The plant materials were washed, thinly sliced, dried under shade, size reduced to powder using mortar and pestle. Five hundred grams (500 g) of the powdered ginger was extracted with 2.5 liters of (70% v/v ethanol) by cold maceration for 72 hours. The extract was evaporated and concentrated to dryness in a water bath at 50^{o}C to obtain the dry crude ethanol extract of ginger (EEG). Similarly, another five hundred grams (500 g) of the powdered ginger was macerated with 2.5 liters of ethyl acetate (100%) for 72 hours, after which it was filtered, concentrated and evaporated to dryness in a water bath at 50^{o}C to obtain the dry crude ethyl acetate extract of ginger (EAEG). The resultant dried extracts were weighed and kept in a refrigerator at 4^{0}C in air tight plastic containers until used for this study. The solutions of the extracts were freshly prepared for each study by dissolving the appropriate amount required in deionized water under standard laboratory conditions.

Experimental design

The studies were carried out using five (5) groups each containing ten or six animals as the case may be for each of the extract evaluated. Two groups received normal saline and a standard drug (sodium valproate or diazepam or phenobarbitone) to serve as negative and positive controls respectively while the remaining three groups received graded doses of the extracts (50, 100 and 200 mg/kg). The ethanol and ethyl acetate extracts of the plant were administered and evaluated for anticonvulsant activity separately. The doses of the extracts were selected based on previous studies (Hosseini and Mirazi, 2015; Hosseini *et al*., 2016). Results obtained for each experiment were recorded accordingly.

Evaluation of anticonvulsant activity

Maximum electroshock (MES)-induced seizure

The anticonvulsant activity of both ethanol and ethyl acetate extracts of *Zingiber officinale* rhizomes was evaluated using the method of Swinyard and Kupferberg (1985) and modified by Browning (1992). Fifty day old chicks were divided randomly into five groups of 10 chicks per group. The first group of animals were administered normal saline (10 ml/kg) which served as negative control. The second, third and fourth groups were treated with 50, 100 and 200 mg/kg of the ethanol extract of *Zingiber officinale* (EEG) while the last group received phenobarbitone (30 mg/kg) which served as positive control. The same procedure was repeated with the ethyl acetate extract of *Zingiber officinale* (EAEG). All the drugs were administered intra-peritoneally. An electroconvulsive machine (Ugo basile, Model 7800) was used to induce seizures. The shock was delivered thirty min after the drugs administration by passing a current of 70 mA, 50 Hz for 0.2 sec duration through the micro dynamometer with corneal electrodes placed on the upper eyelids of the chicks. The chicks were observed for hind limb tonic extension which was considered as convulsion while abolition of hind limb tonic extension was considered as protection against electrically induced convulsion.

Pentylenetetrazole (PTZ)-induced seizure in mice

The method previously described by Swinyard et al., (1989) was used in this study. Thirty mice were randomly divided into five groups each containing six mice. The first group received normal saline (10 ml/kg). The second, third and fourth groups were treated with 50, 100 and 200 mg/kg of the ethanol extract of *Zingiber officinale* (EEG) while sodium valproate (200 mg/kg) was administered to the positive control group. All the drugs were administered intraperitoneally. Thirty minutes after the drugs administration, the mice in all the groups received freshly prepared pentylenetetrazole (85mg/kg) subcutaneously. The procedure was repeated with the ethyl acetate extract of *Zingiber officinale* (EAEG). The mice were observed for presence or absence of clonic spasm of at least 5 seconds duration, hind limb extension, the onset of seizures or death.

Strychnine-induced seizure in mice

The method previously described by Porter et al., (1984) was employed. Thirty mice were randomly divided into five groups each containing six mice. The first group received normal saline (10 ml/kg) while the second, third and fourth groups were treated with 50, 100 and 200 mg/kg of the ethanol extract of *Zingiber officinale* (EEG). The fifth group received diazepam (20 mg/kg) and served as the positive control. All the drugs were administered intraperitoneally. Thirty minute after pretreatment, mice in all the groups were administered with freshly prepared strychnine (2 mg/kg) subcutaneously. This procedure was repeated with the ethyl acetate extract of *Zingiber officinale* (EAEG). The mice were observed for tonic extensor jerks of the hind limb which was considered as convulsion and abolition of such was considered as protection.

Statistical analysis

Results were expressed as the Mean ± Standard Error of the Mean (SEM) and percentages. Data were analyzed using statistical package for the Social Sciences (SPSS) version 23. The difference between the control and the test groups were analyzed for statistical significance using One Way ANOVA followed by Bonferroni's post hoc t-test for multiple comparisons. Values of $p \leq 0.05$ were considered significant.

Results

Effect of ethanol and ethyl acetate extracts of Zingiber officinale against MES in mice

Both ethanol and ethylacetate extracts of *Zingiber officinale* at the doses of 100 and 200 mg/kg produced a dose-dependent protection against MES-induced tonic hind limb extension seizure in chicks, while phenobarbitone 30 mg/kg demonstrated 100% protection against seizure. However, the ethanol extract produced better protection at all doses tested comparing the 40% to 10%, 70% to 50% and 80% to 60% at 50, 100, and 200 mg/kg respectively (fig.1).

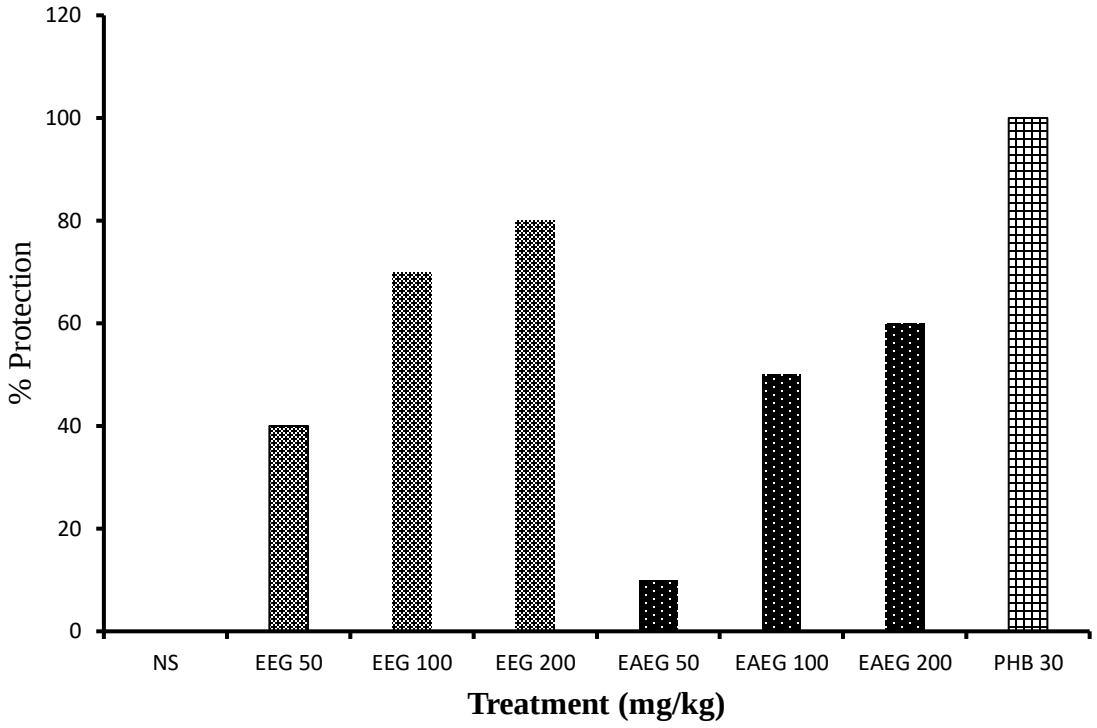

Fig.1: Effect of ethanol and ethyl acetate extracts of *Zingiber officinale* (ginger) against maximal electroshock induced seizure in chicks. n= 10, EEG= Ethanol extract of ginger, EAEG= Ethyl acetate extract of ginger, NS= Normal saline.

Effect of ethanol and ethyl acetate extracts of Zingiber officinale against PTZ-induced seizure in mice

Both ethanol and ethyl acetate extracts of *Zingiber officinale* at the doses of 100 and 200 mg/kg significantly ($p<0.001$) prolonged the mean time of death from PTZ-induced seizure. In addition, the extracts at the doses of 100 and 200 mg/kg significantly ($p<0.05$) decreased the onset of seizure against PTZ-induced seizure. However, sodium valproate 200 mg/kg significantly ($p<0.001$) decreased the onset of seizure and demonstrated 100% protection against mortality (fig.2).

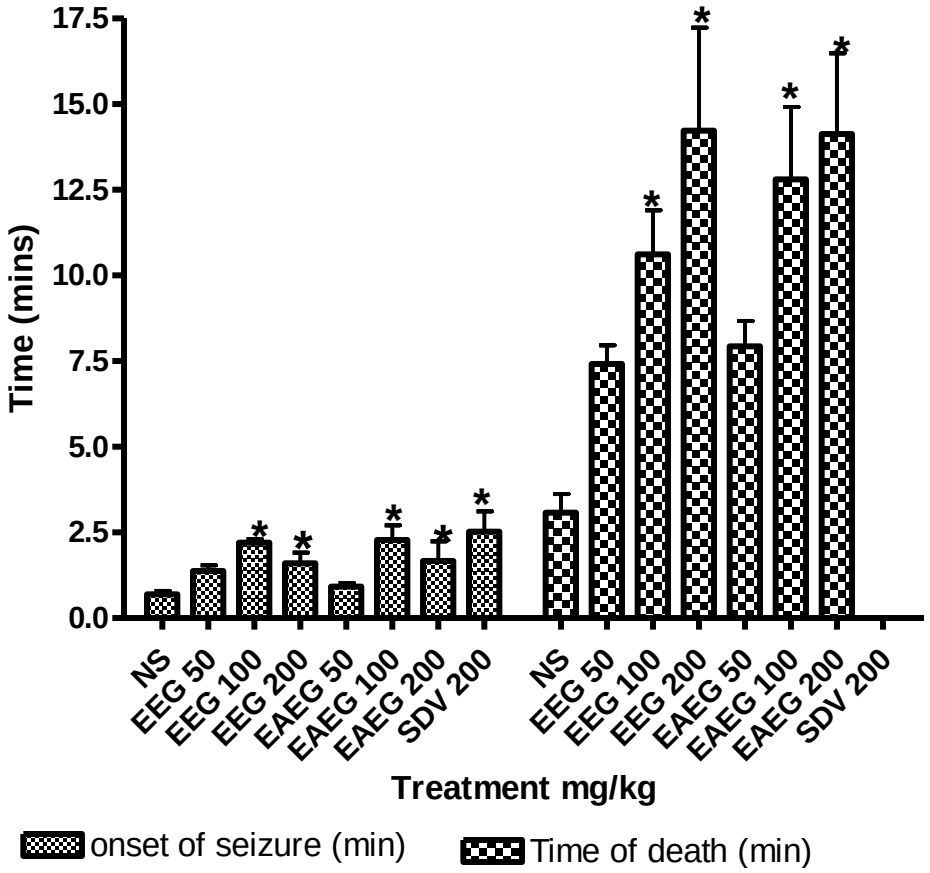

Fig.2: Effect of ethanol and ethyl acetate extracts of *Zingiber officinale* (ginger) against PTZ-induced seizure in mice. n= 6, EEG= Ethanol extract of ginger, EAEG= Ethyl acetate extract of ginger, NS= Normal saline 10 ml/kg. $p \leq 0.01$

Effect of ethanol and ethyl acetate extracts of Zingiber officinale against strychnine-induced seizure in mice

Both ethanol and ethyl acetate extracts of *Zingiber officinale* at all the doses tested significantly ($p<0.01$) decreased the onset of strychnine-induced clonic seizure in mice, but the effect of ethanol extract at 100 and 200 mg/kg was more significant ($p<0.001$). Similarly, diazepam 20 mg/kg significantly ($p< 0.01$) decreased the onset of seizure (fig.3). However, there was no significant difference in the mean time of death between the control (normal saline) and all the treatment groups.

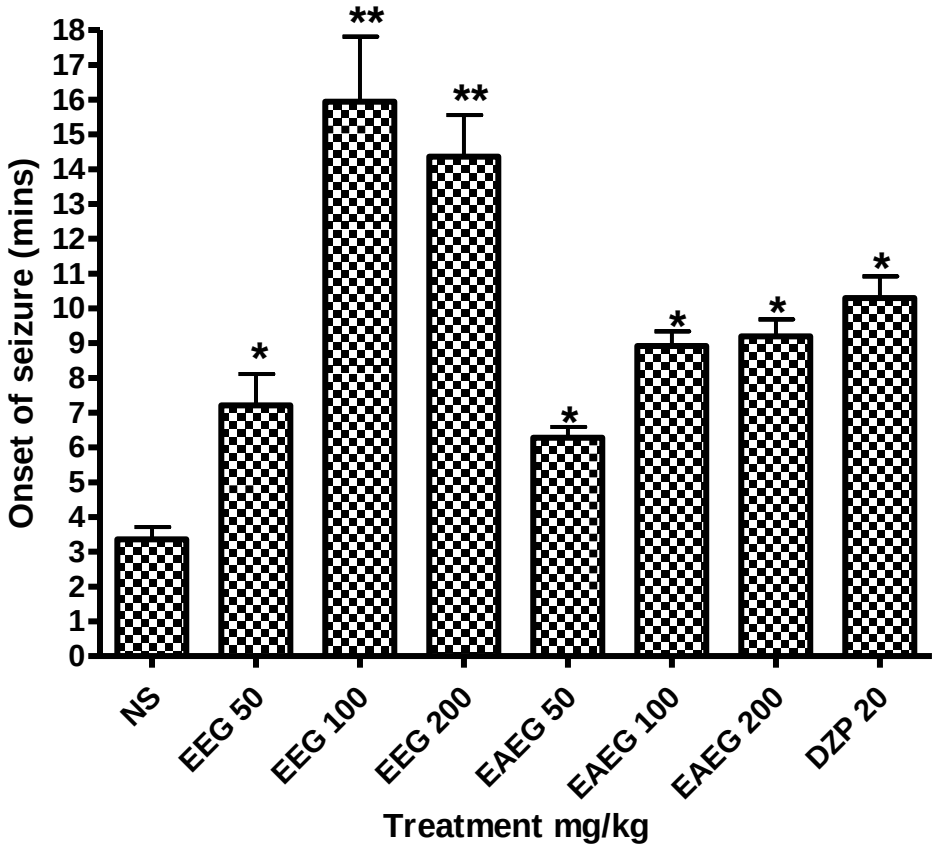

Fig 3: Effect of ethanol and ethyl acetate extracts of *Zingiber officinale* (ginger) against strychnine-induced seizure in mice. n= 6, EEG= Ethanol extract of ginger, EAEG= Ethyl acetate extract of ginger, NS= Normal saline 10 ml/kg. *$p \leq 0.01$, ** $p \leq 0.001$

Discussion

In extracting bioactive compounds from plant materials to promote human health and treat various diseases, it is very important that the most appropriate solvent is chosen. This is because, the pharmacological activity of the resultant extract would be significantly affected by the solvent used for the extraction process. In the present study, the anticonvulsant activity of ginger extracts obtained from a relatively more polar solvent (ethanol) was compared with that of a relatively more non-polar solvent (ethyl acetate) using three of the commonly used animal models for screening antiepileptic drugs; maximal electroshock- (MES), pentylenetetrazole- (PTZ) and strychnine-induced seizures.

The results presented here revealed that both ethanol and ethyl acetate extracts of *Zingiber officinale* (ginger) contain neuroactive compounds that could be beneficial in the management of epilepsy. In maximal electroshock-induced seizure (MES) model, the extracts demonstrated a dose-dependent protection against tonic hind limb extension seizure. However, the lowest dose of the ethanol extract administered produced a 40% protection against seizure while that of the ethyl acetate was only 10%. Similarly, at the highest dose of the ethanol extract, there was 80% protection compared to the 60%

protection produced by the ethyl acetate extract. The MES model in animal is widely believed to represent generalized tonic clonic type of seizure or gland mal type of epilepsy (Gupta et al., 2013). The abolition of tonic-clonic seizure by these extracts is an indication of their anticonvulsant activity.

Some of the currently available standard drugs such as phenobarbital, phenytoin, lamotrogine and carbamazepine used in the management of epilepsy exhibited their effects against seizures induced by MES via gama-aminobutyric acid (GABA) pathway (Gupta et al., 2013). Therefore, any compounds with the ability to suppress the hind limb tonic extension (HLTE) in the MES and prevent the spread of seizure in the brain would be beneficial in the management of generalized tonic-clonic and partial seizures (Browning, 1992; Gupta et al., 2013). Data obtained in this study suggest that ethanol and ethyl acetate extracts of *Zingiber officinale* contain compound (s) with anticonvulsant activity.

PTZ-induced seizure test is widely considered a good model for measuring the anticonvulsant activity of compounds against absence seizures and used to identify compounds that can raise seizure threshold in the brain (White et al., 1998; Kar et al., 2014). Previously, aqueous-ethanolic extract of *Zingiber officinale* was shown to exert anticonvulsant activity in the PTZ-induced seizure test in mice (Hosseini and Mirazi, 2014; Hosseini and Mirazi, 2015). In the present study, both the ethanol and ethyl acetate extracts of *Zingiber officinale* exhibited significant ($p<0.05$) anticonvulsant activity against PTZ-induced seizure in mice. PTZ is known to induce seizure by interacting with the GABA neurotransmission (inhibition) and enhancing excitatory effects in the brain (Gupta et al., 2013). Phenobarbital, valproate and diazepam are examples of antiepileptic drugs known to exert their effects by enhancing GABA-mediated inhibition in the brain (Porter & Meldrum, 2001). The findings of this study suggest that the extracts might have protected against PTZ-induced seizure probably by interfering with GABAergic neurotransmission. The ability of the extracts to protect the animals against PTZ-induced seizure suggests anticonvulsant potential against absence /petit mal or myoclonic seizures. Thus, the ethanol and ethyl acetate extracts of *Zingiber officinale* may be useful in the management of absence and/or myoclonic seizure.

Strychnine is known to induce convulsion or seizure by interfering with glycine mediated post-synaptic inhibition at the glycine receptors (Kar et al., 2014). It induces excitatory effect on the central nervous system by blocking glycine uptake at the spinal cord neurons, resulting in seizure induction (Elmowafy and Dayem, 2021). Glycine is a major inhibitory neurotransmitter of the motor neurons and interneurons in the spinal cord (Ya'u et al., 2015). Results from the present study shows that both ethanol and ethyl acetate extracts of *Zingiber officinale* protected against strychnine-induced seizure in mice. The ability of these extracts to protect mice against strychnine-induced seizure is an indication that their anticonvulsant effects might have been mediated via glycine receptors by raising seizure latency in the spinal cord.

The rhizomes of *Zingiber officinale* (Ginger) are very rich in different metabolites, from different types of terpenes to phenolic compounds (Koch et al., 2017). Previous phytochemical studies have revealed the presence of more than 400 different compounds, including terpenes, flavonoids, saponins, phlobatannin, anthraquinones, the

pungent oleo-resin compounds, phenolic compounds such as gingerol, paradols, and shogaol (Ajayi et al., 2013; Prasad and Tyagi, 2015; Wakchaure and Ganguly, 2018). The gingerols and shogaol are the major bioactive constituents of ginger (Prasad and Tyagi, 2015). Besides, many of the medicinal effects of ginger have been attributed to the presence of bioactive compounds like gingerols, shogaols, paradols, gingerdiols, and zingerone (Baliga et al., 2013). Previous studies proved that gingerols and shogaols cross the blood–brain barrier, exhibit CNS activity and have neuroprotective effect (Ha et al., 2012; Kukula-Koch et al., 2018; Simon et al., 2020). Also, the oleo resins and phenolic compounds are thought to be responsible for the anticonvulsant effect of ginger (Tamson *et al.*, 2012). From the results obtained in this study, it can be said that the ethanol extract of *Zingiber officinale* produced a better anticonvulsant activity compared to ethyl acetate extract. This may be due to the fact that the oleo resins and polyphenols present in ginger are largely more soluble in ethanol solvent than ethyl acetate solvent.

Conclusion

From the results of this study, it can be concluded that both ethanol and ethyl acetate extracts of *Zingiber officinale* contain biologically active compounds with significant anticonvulsant activity, but the ethanol extract produced a better anticonvulsant activity.

Acknowledgments

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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